A Versatile and Efficient Synthesis of 2-Alkyl and 2-Aryl-6-alkyl-2,3-dihydro-1*H*-pyridin-4-ones

Nicolas Leflemme, Patrick Dallemagne,* Sylvain Rault

Centre d'Etudes et de Recherche sur le Medicament de Normandie, UFR des Sciences Pharmaceutiques, 1 rue Vaubénard 14032 CAEN Cedex, France
Fax +33(2)31931188; E-mail: dallemagne@pharmacie.unicaen.fr

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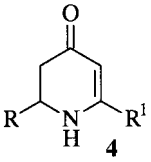
Abstract: A versatile and efficient method for the preparation of 2-alkyl and 2-aryl-6-alkyl-2,3-dihydro-1*H*-pyridin-4-ones is described. The sequence involved the condensation of β-amino acids and *t*-butyl ketoester to give enaminoesters whose intramolecular cyclisation followed by an hydrolysis step afforded the expected products.

Key words: β-amino ester, enaminoester, dihydropyridinone, ring closure, heterocycle

Dihydropyridinones are interesting building blocks for a large variety of heterocycle syntheses because their aminoenone moiety can be used in various reactions leading to key intermediates particularly useful in the synthesis of alkaloids and pharmacologicaly active agents.[1] Further, we have recently pointed out the interest of the dihydropyridinones of the type **1** (Scheme 1) as memory enhancers in relation to their nicotinic acetylcholine receptor affinity.[2] Two general methods for synthesizing these compounds have been reported. The first consists in applying Comins' methodology by the use of organometallics and 1-acyl salts of 4-methoxypyridines,[3] the second employed a Schiff base and a β-diketone in the presence of potassium amide in liquid ammonia.[4] Recently, we developed a new method for the synthesis of **1** starting from β-aryl-β-amino acids **2** converted in four steps into the hydrochloric salts of δ-aryl-δ-amino-β-ketoketones **3** before being cyclised to **1** (Scheme 1).[5] In spite of the versatility of this method and the good yields obtained, the use of powdered samarium limited the quantities of starting material and we therefore sought an alternative method to achieve the desired conversion.

The method we now describe was developed starting from the same β-amino acids **2** and leads in four steps to the attempted dihydropyridinones **4** by adapting a method very recently described by Ma[6] in a preliminary report.

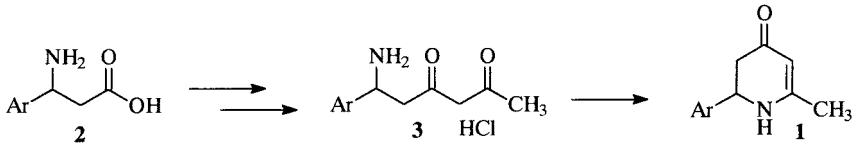
Apart from its implementation on great quantities of starting material the other interest of this method lies in the possibility of introducing in position 6 various others substituents than the methyl group (Scheme 2).



Scheme 2

The reaction sequence proposed by Ma[6] involved the acetate salts of β-amino esters **5** which were condensed with ethyl β-ketoesters. The intermediates were cyclized with sodium ethoxide to afford **6** whose the ester moiety was removed by treatment in a mixture of ethanol and aqueous sodium hydroxide to give the dihydropyridinones **4** (Scheme 3). Because of the difficulties encountered during the application of this method to our compounds and in particular because of the low yields obtained during the hydrolysis of the ethyl carboxylate group we preferred to replace the ethyl β-ketoesters by *t*-butylesters.

The acetate salts of the β-aryl-β-amino esters **7a**–**c** were readily prepared via an esterification step of the corresponding β-aryl-β-amino acids **2a**–**c**,[7] using thionyl chloride in ethanol. The hydrochloric salts thus obtained were then displaced with ammonia and converted into the desired acetate salts **7a**–**c** by the use of acetic acid (Scheme 4).



Scheme 1

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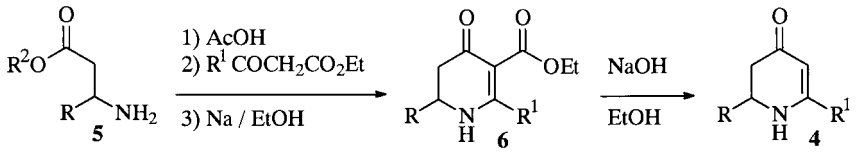
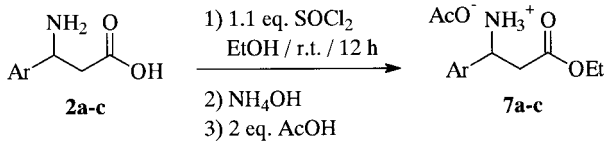
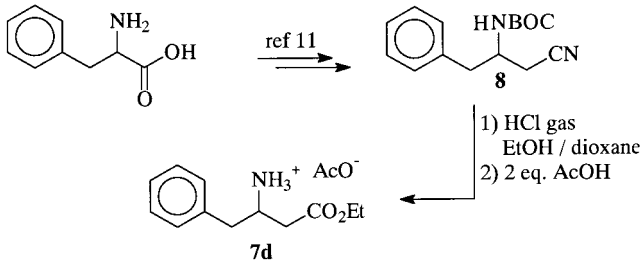


Scheme 3



Scheme 4

The required acetate salt of β-homophenylalanine ethyl ester **7d** was prepared from α-phenylalanine as shown in Scheme 5. Among the numerous methods for the conversion of an α-amino acid to its homologous β-amino acid, including the Arndt-Eistert reaction,[8] the opening of aziridine-2-carboxylates[9] and a more recently described procedure via $BtCH_2TMS$,[10] we favored an approach involving nucleophilic displacement of a tosylate by cyanide.[11] Under acidic condition, in ethanol, the resulting nitrile **8** was hydrolyzed and the BOC group was removed. The corresponding β-amino ester was finally reacted with acetic acid to give the acetate salt **7d** (Table 1).



Scheme 5

Table 1 Preparation of Acetates **7a–d**

Product	R	Yield (%)	Mp (°C)
7a	Ph	95	97
7b	3-ClPh	93	94
7c	Py	92	62
7d	Bn	63	86

The resulting acetate salts **7a–d** were then treated either by *t*-butylacetoacetate or *t*-butylpropionylacetate in the presence of an equivalent amount of acetic acid in refluxing benzene with azeotropic removal of water to give the enamino esters **9–12** in good yields after purification (Scheme 6, Table 2). As Baraldi has described for the preparation of enaminones[12] and as we checked by using hydrochloric salts of β-amino ester instead of the acetates, the reaction was slower and did not go to completion in the absence of acetic acid.

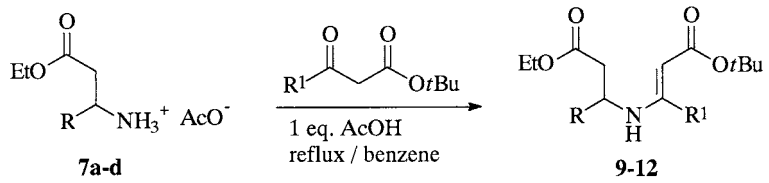
The enaminoesters **9–12** were then cyclized with potassium *t*-butoxide in *t*-butanol to afford the *t*-butyl 4-ketodihydropyridine-3-carboxylates **13–16** (Scheme 7).[13] Removal of the *t*-butyl ester group of the latter was finally performed by refluxing in dichloromethane in the presence of TFA to give the title 2,6-disubstituted-2,3-dihydropyridin-4-ones **17–20** in high yields (Table 3).

In summary, we have developed a versatile and efficient methodology for the preparation of 2-alkyl or 2-aryl-6-alkyl-2,3-dihydro-1*H*-pyridin-4-ones. The interaction of these new compounds with the neuronal nicotinic receptor and their pharmacological properties is now under investigation.

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. The NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 with a JEOL Lambda 400 spectrometer, the chemical shifts (δ) are expressed in ppm relative to TMS for ^1H and ^{13}C nuclei, the coupling constants (*J*) are given in Hz, conventional abbreviations are used. IR spectra were recorded on a Genesis Series FTIR spectrometer. A typical example of IR spectrum is given for each series of compounds. Element microanalyses were obtained from the 'Institut de Recherche en Chimie Fine' (Rouen). Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAN SIL G/UV_{254}) with viualization by UV irradiation. Silica gel 60 (70–230 mesh) was ued for column chromatography. Petroleum ether (PE) used had a bp 40–60°C.

Table 2 Preparation of Enamino Esters **9–12**

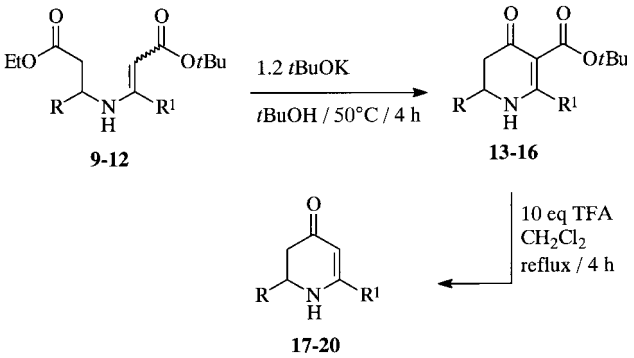
Product	R	R^1	Yield (%)
9a	Ph	Me	85
9b	Ph	Et	80
10a	3-ClPh	Me	82
10b	3-ClPh	Et	86
11a	Py	Me	80
11b	Py	Et	82
12	Bn	Me	81



Scheme 6

Ethyl 3-Amino-3-arylpropanoate Acetate 7a-c, General Procedure

$SOCl_2$ (0.44 mL, 6 mmol) was added dropwise to a soln of β-amino acid **2** (5 mmol) in EtOH (20 mL) cooled in an ice-bath. The mixture was stirred for 12 h at r.t. After removal of solvent, the residue was poured into H_2O (20 mL), neutralized with NH_4OH and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($CaCl_2$), and concentrated in vacuo. The crude amino ester was dissolved in MeOH (10 mL), and HOAc (0.57 mL, 10 mmol), was added. The mixture was stirred for 0.5 h at r.t. and the solvents were removed in vacuo. Recrystallization in an appropriate solvent yielded the product as white powder.



Scheme 7

Ethyl 3-amino-4-phenylbutanoate acetate (7d)

A stirred soln of 3-[(*t*-butoxycarbonyl)amino]-4-phenylbutanenitrile **8** (10 mmol), in anhyd EtOH (10 mL) and anhyd dioxane (10 mL) was saturated with HCl gas. The mixture was refluxed for 12 h and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 10% aq $NaHCO_3$ (2 × 20 mL), dried over $CaCl_2$ and concentrated in vacuo. The crude amino ester was dissolved in MeOH (10 mL), and HOAc (0.92 mL,16 mmol) was added. The mixture was stirred for 0.5 h at r.t. and the solvents were removed in vacuo. Recrystallization with appropriated solvent yielded the product as white powder.

The ^1H and ^{13}C NMR data of **7** are recorded in Table 4. Satisfactory microanalyses were obtained for **7a**–**d**, C ± 0.40, H ± 0.29, N ± 0.33.

7a

IR (KBr): 3190, 3055, 2977, 2883, 1736, 1601, 1519, 1439, 1382, 1248, 1193, 789, 695 cm^{-1}.

***tert*-Butyl 3-(1-Alkyl or Aryl-3-ethoxy-3-oxopropylamino)but-2-enoate 9a,10a,11a,12 and *tert*-Butyl 3-(1-Aryl-3-ethoxy-3-oxopropylamino)pent-2-enoate 9b,10b,11b; General Procedure**

To a stirred suspension of acetate **7a**–**d** (5 mmol), in anhyd benzene (20 mL), was added HOAc (0.29 mL, 5 mmol), and β-ketoester (6 mmol). The mixture was heated under reflux and the H_2O formed was removed azeotropically using a Dean–Stark apparatus. After cooling to r.t., $CHCl_3$ (25 mL) was added and the soln was washed with sat. $NaHCO_3$ soln (2 × 20 mL). The organic layer was dried ($CaCl_2$), the solvents were removed in vacuo and the residue was purified by chromatography on silica gel eluting with variable amounts of Et_2O–PE to give the pure corresponding enamine. The

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Table 3 Preparation of 2,6-Disubstituted-2,3-dihydropyridin-4-ones **17–20**

Product	R	R^1	Yield (%)	Mp (°C)	Product	Yield (%)	Mp (°C)
13a	Ph	Me	85	163	**17a**	92	160
13b	Ph	Et	78	104	**17b**	93	141
14a	3-ClPh	Me	84	207	**18a**	94	160
14b	3-ClPh	Et	84	76	**18b**	93	132
15a	Py	Me	84	172	**19a**	78	148
15b	Py	Et	79	102	**19b**	79	96
16	Bn	Me	84	119	**20**	92	96

Table 4 ^{1}H and ^{13}C NMR Data of Compounds **7a**–**d**

Product	^{1}H NMR (DMSO-d_6), δ, *J* (Hz)	^{13}C NMR (DMSO-d_6), δ, *J* (Hz)
7a	1.04 (t, 3 H, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.84 (s, 3 H, CH$_3$C=O), 2.84 (dd, 1 H, *J* = 8.3, 15.6 Hz, C*H*HC=O), 3.01 (dd, 1 H, *J* = 5.8, 15.6 Hz, CH*H*C=O), 3.95 (q, 2 H, *J* = 7.0 Hz, CH$_3$C*H*$_2$O), 4.47 (dd, 1 H, *J* = 5.8, 8.3 Hz, CH), 7.29–7.45 (m, 5 H, C$_6$H$_5$), 9.49 (br s, 3 H, NH$_3$)	14.0 (*C*H$_3$CH$_2$O), 22.1 (*C*H$_3$C=O), 40.4 (*C*H$_2$C=O), 51.6 (CH), 60.4 (CH$_3$*C*H$_2$O), 127.5 128.4 128.7 (*C*HAr), 139.5 (CAr), 169.9 (C=O), 173.5 (CH$_3$*C*=O)
7b	1.10 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.86 (s, 3 H, C*H*$_3$C=O), 2.61 (dd, 1 H, *J* = 6.6, 15.3 Hz, C*H*HC=O), 2.68 (dd, 1 H, *J* = 7.7, 15.3 Hz, CH*H*C=O), 3.99 (q, 2 H, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 4.25 (dd, 1 H, *J* = 6.6, 7.7 Hz, C*H*), 7.26–7.47 (m, 4 H, C$_6$*H*$_4$Cl), 9.21 (br s, 3 H, N*H*$_3$)	13.9 (*C*H$_3$CH$_2$O), 21.6 (*C*H$_3$C=O), 43.1 (*C*H$_2$C=O), 51.9 (*C*H), 59.8 (CH$_3$*C*H$_2$O), 125.3, 126.5, 126.8, 129.9 (*C*HAr), 132.9, 147.3 (*C*Ar), 170.7 (*C*=O), 172.6 (CH$_3$*C*=O)
7c[a]	1.24 (t, 3 H, *J* = 6.9 Hz, C*H*$_3$CH$_2$O), 2.06 (s, 6 H, C*H*$_3$C=O), 2.73 (dd, 1 H, *J* = 4.3, 16.2 Hz, C*H*HC=O), 2.82 (dd, 1 H, *J* = 8.7, 16.2 Hz, CH*H*C=O), 4.14 (q, 2 H, *J* = 6.9 Hz, CH$_3$C*H*$_2$O), 4.53 (dd, 1 H, *J* = 4.3 8.7 Hz, CH), 5.69 (br s, 3 H, NH$_3$), 7.35 (dd, 1 H, *J* = 3.5, 7.2 Hz, ArH), 7.83 (d, 1 H, *J* = 7.2 Hz, *H*Ar), 8.54 (d, 1 H, *J* = 3.5, ArH), 8.63 (s, 1 H, ArH)	13.7 (*C*H$_3$CH$_2$O), 21.8 (*C*H$_3$C=O), 38.6 (*C*H$_2$C=O), 49.3 (*C*H), 61.1 (CH$_3$*C*H$_2$O), 124.0 (*C*HAr), 133.6 (CAr), 135.4, 147.9, 148.8 (*C*HAr), 169.8 (C=O), 176.5 (CH$_3$*C*=O)
7d[a]	1.24 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 2.02 (s, 3 H, CH$_3$C=O), 2.62 (m, 2 H, CH$_2$C=O), 2.86 (dd, 1 H, *J* = 8.5, 13.3 Hz, C*H*HPh), 3.07 (dd, 1 H, *J* = 6.1 13.3 Hz, CH*H*Ph), 3.68 (m, 1 H, CH), 4.13 (q, 2 H, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 7.20–7.34 (m, 5 H, C$_6$H$_5$), 8.38 (br s, 3 H, NH$_3$)	13.8 (*C*H$_3$CH$_2$O), 22.4 (*C*H$_3$C=O), 35.5 (*C*H$_2$Ph), 38.8 (*C*H$_2$C=O), 49.4 (CH), 60.9 (CH$_3$*C*H$_2$O), 127.0, 128.7, 129.2 (*C*HAr), 135.7 (CAr), 171.1 (C=O), 176.8 (CH$_3$*C*=O)

[a] ^{1}H and ^{13}C NMR in CDCl$_3$.

^{1}H and ^{13}C NMR data of **9**,**10**,**11**,**12** are recorded in Table 5. Satisfactory microanalyses were obtained for **9a**–**b**,**10a**–**b**,**11a**–**b**,**12** C ± 0.40, H ± 0.25, N ± 0.24.

9a
IR (KBr): 3275, 3194,2977, 2930, 1736, 1649, 1613, 1451, 1366, 1264, 1152, 770, 699 cm^{-1}.

Table 5 ^{1}H and ^{13}C NMR Data of Compounds **9**–**12**

Product	^{1}H NMR (CDCl$_3$), δ, *J* (Hz)	^{13}C NMR (CDCl$_3$), δ, *J* (Hz)
9a	1.16 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 1.43 [s, 9 H, C(CH$_3$)$_3$], 1.75 (s, 3 H, CH$_3$), 2.70 (dd, 1 H, *J* = 6.4, 15.4 Hz, C*H*HC=O), 2.76 (dd, 1 H, *J* = 8.4, 15.4 Hz, CH*H*C=O), 4.03 (dq 1 H, *J* = 7.2, 10.7 Hz, CH$_3$C*H*HO), 4.10 (dq, 1 H, *J* =7.2, 10.7 Hz, CH$_3$CH*H*O), 4.37 (s, 1 H, C=CH), 4.95 (m, 1 H, CH), 7.20–7.30 (m, 5 H, C$_6$H$_5$), 8.97 (d, 1 H, *J* = 8.8 Hz, NH)	14.0 (*C*H$_3$CH$_2$O), 19.5 (CH$_3$), 28.5 [C(*C*H$_3$)$_3$], 43.4 (*C*H$_2$C=O), 53.9 (CH), 60.8 (CH$_3$*C*H$_2$O), 77.9 [*C*(CH$_3$)$_3$], 85.9 (C=*C*H), 125.8 127.4 128.7 (*C*HAr), 142.1 (CAr), 160.0 (*C*=CH), 170.3 (C=O), 170.5 (C=O)
9b	1.02 (t, 3 H, *J* = 7.6 Hz, CH$_2$C*H*$_3$), 1.21 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.49 [s, 9 H C(CH$_3$)$_3$], 2.02 (dq, 1 H, *J* = 7.6, 15.2 Hz, C*H*HCH$_3$), 2.19 (dq, 1 H, *J* = 7.6, 15.2 Hz, CH*H*CH$_3$), 2.74–2.82 (m, 2 H CH$_2$C=O), 4.10 (dq, 1 H, *J* = 7.1, 10.8 Hz, CH$_3$C*H*HO), 4.14 (dq, 1 H, *J* =7.1, 10.8 Hz, CH$_3$CH*H*O), 4.45 (s, 1 H, C=CH), 5.01 (m, 1 H, CH), 7.26–7.36 (m, 5 H C$_6$H$_5$), 9.05 (d, 1 H, *J* = 9.2 Hz, NH)	11.8 (CH$_2$*C*H$_3$), 14.0 (*C*H$_3$CH$_2$O), 25.0 (*C*H$_2$CH$_3$), 28.2 [C(*C*H$_3$)$_3$], 43.3 (*C*H$_2$C=O), 52.9 (CH), 60.3 (CH$_3$*C*H$_2$O), 78.9 [*C*(CH$_3$),$_3$], 84.4 (C=*C*H), 125.7 127.9 128.5 (*C*HAr), 141.6 (CAr), 163.9 (*C*=CH), 170.2 (C=O), 170.5 (C=O)
10a	1.19 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.45 [s, 9 H, C(CH$_3$)$_3$], 1.76 (s, 3 H, CH$_3$), 2.70 (dd, 1 H, *J* = 5.8, 15.4 Hz, C*H*HC=O), 2.76 (dd, 1 H, *J* = 8.3, 15.4 Hz, CH*H*C=O), 4.07 (dq, 1 H, *J* = 7.2, 10.8 Hz, CH$_3$C*H*HO), 4.11 (dq, 1 H, *J* =7.2, 10.8 Hz, CH$_3$CH*H*O), 4.42 (s, 1 H, C=CH), 4.93 (m, 1 H, CH), 7.13–7.22 (m, 4 H, C$_6$H$_4$Cl), 8.96 (d, 1 H, *J* = 8.6 NH)	14.0 (*C*H$_3$CH$_2$O), 19.5 (CH$_3$), 28.5 [C(*C*H$_3$)$_3$], 43.2 (*C*H$_2$C=O), 53.5 (CH), 60.9 (CH$_3$*C*H$_2$O), 78.2 [*C*(CH$_3$)$_3$], 86.7 (C=*C*H), 124.1 126.2 127.7 130.1 (*C*HAr), 134.6 144.3 (CAr), 159.6 (*C*=CH), 170.1 (C=O), 170.3 (C=O)

Table 5 ^{1}H and ^{13}C NMR Data of Compounds **9**–**12** (continued)

Product	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ, *J* (Hz)
10b	0.94 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.13 (t, 3 H, *J* = 7.1 Hz, CH_3CH_2O), 1.41 [s, 9 H, $C(CH_3)_3$], 1.92 (dq, 1 H, *J* = 7.6, 15.2 Hz, CHHCH$_3$), 2.08 (dq 1 H, *J* = 7.6, 15.2 Hz, CHHCH$_3$), 2.64 (dd, 1 H, *J* = 5.9, 15.4 Hz, CHHC=O), 2.69 (dd, 1 H, *J* = 8.2, 15.4 Hz, CHHC=O), 4.02 (dq, 1 H, *J* = 7.1, 10.9 Hz, CH_3CHHO), 4.06 (dq, 1 H, *J* =7.1, 10.9 Hz, CH_3CHHO), 4.41 (s, 1 H, C=CH), 4.90 (m, 1 H, CH), 7.09–7.22 (m, 4 H, C_6H_4Cl), 8.95 (d, 1 H, *J* = 9.3 Hz, NH)	11.8 (CH_2CH_3), 13.9 (CH_3CH_2O), 25.1 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 43.4 (CH_2C=O), 52.9 (CH), 60.8 (CH_3CH_2O), 78.1 [$C(CH_3)_3$], 84.9 (C=CH), 123.9 126.1 127.5 130.0 (CHAr), 134.5 144.5 (CAr), 164.8 (C=CH), 170.1 (C=O), 170.6 (C=O)
11a	1.22 (t, 3 H, *J* = 7.2 CH_3CH_2O), 1.48 [s, 9 H $C(CH_3)_3$], 1.81 (s, 3 H CH_3), 2.78 (dd, 1 H *J* = 6.0, 15.4 Hz, CHHC=O), 2.85 (dd, 1 H *J* = 8.2, 15.4 Hz, CHHC=O), 4.10 (dq 1 H *J* = 7.2, 10.7 Hz, CH_3CHHO), 4.13 (dq 1 H *J* =7.2, 10.7 Hz, CH_3CHHO), 4.46 (s, 1 H, C=CH), 5.04 (m, 1 H, CH), 7.30 (dd, 1 H, *J* = 3.9, 7.6 Hz, ArH), 7.64 (dd, 1 H, *J* = 1.3, 7.8 Hz, ArH), 8.53 (d 1 H, *J* = 3.9 Hz, ArH), 8.57 (d 1 H, *J* = 1.3 Hz, ArH), 9.04 (d 1 H, *J* = 8.8 Hz, NH)	13.9 (CH_3CH_2O), 19.4 (CH_3), 28.4 [$C(CH_3)_{,3}$], 42.9 (CH_2C=O), 51.6 (CH), 60.9 (CH_3CH_2O), 78.2 [$C(CH_3)_3$], 86.8 (C=CH), 123.6, 133.5 (CHAr), 137.5 (CAr), 147.9, 148.9 (CHAr), 159.3 (C=CH), 169.9 (C=O), 170.2 (C=O)
11b	1.04 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.22 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 1.49 [s, 9 H, $C(CH_3)_3$], 2.02 (dq 1 H, *J* = 7.5, 15.0 Hz, CHHCH$_3$), 2.20 (dq 1 H, *J* = 7.6, 15.2 Hz, CHHCH$_3$), 2.78 (dd, 1 H, *J* = 5.9, 15.5 Hz, CHHC=O), 2.84 (dd, 1 H, *J* = 8.4, 15.5 Hz, CHHC=O), 4.11 (dq 1 H, *J* = 7.2, 10.7 Hz, CH_3CHHO), 4.15 (dq 1 H, *J* =7.1 10.8 Hz, CH_3CHHO), 4.49 (s, 1 H, C=CH), 5.06 Hz, (m, 1 H, CH), 7.29 (dd, 1 H, *J* = 4.6, 7.7 Hz, ArH), 7.64 (dd, 1 H, *J* = 1.7, 7.7 Hz, ArH), 8.53 (d, 1 H, *J* = 4.6 Hz, ArH), 8.57 (d, 1 H, *J* = 1.7 Hz, ArH), 9.07 (d, 1 H, *J* = 9.4 Hz, NH)	11.8 (CH_2CH_3), 13.9 (CH_3CH_2O), 25.1 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 43.1 (CH_2C=O), 51.1 (CH), 60.9 (CH_3CH_2O), 78.2 [$C(CH_3)_3$], 85.1 (C=CH), 123.6 133.5 (CHAr), 137.7 (CAr), 147.8 148.8 (CHAr), 164.5 (C=CH), 169.9 (C=O), 170.5 (C=O)
12	1.20 (t, 3 H, *J* = 7.1, CH_3CH_2O), 1.44 [s, 9 H, $C(CH_3)_3$], 1.60 (s, 3 H, CH_3), 2.44 (dd, 1 H, *J* = 8.2, 15.6 Hz, CHHC=O), 2.53 (dd, 1 H, *J* = 5.3, 15.6 Hz, CHHC=O), 2.74 (dd, 1 H, *J* = 8.0, 13.6 Hz, CHHPh), 2.79 (dd, 1 H, *J* = 6.1, 15.6 Hz, CHHPh), 4.07–4.10 (m, 3 H, CH, CH_3CH_2O), 4.23 (s, 1 H, C=CH), 7.12–7.26 (m, 5 H, C_6H_5), 8.52 (d, 1 H, *J* = 5.6 Hz, NH)	14.0 (CH_3CH_2O), 19.1 (CH_3), 28.5 [$C(CH_3)_3$], 40.6 (CH_2Ph), 43.0 (CH_2C=O), 51.7 (CH), 60.5 (CH_3CH_2O), 77.6 [$C(CH_3)_3$], 84.6 (C=CH), 126.5 128.2 129.3 (CHAr), 137.5 (CAr), 166.2 (C=CH), 170.3 (C=O), 170.9 (C=O)

***tert*-Butyl 6-Alkyl and 6-Aryl-2-alkyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate 13,14,15,16; General Procedure**

To a stirred soln of enamine **9,10,11,** or **12** (5 mmol), in anhyd *t*-BuOH (10 mL), was added *t*-BuOK (0.67 g 6 mmol), and the mixture was heated at 50 °C. After completion (4 h monitored by TLC analysis), the reaction mixture was quenched with HCl 10% (10 mL), poured into H_2O (10 mL), and extracted with $CHCl_3$ (2 × 20 mL). The combined organic fractions were dried ($CaCl_2$), and concentred in vacuo. The crude product was chromatographed on silica gel eluting with variable amounts of EtOAc–MeOH to give the pure compound. The ^{1}H and ^{13}C NMR data of **13,14,15,16** are recorded in Table 6. Satisfactory microanalyses were obtained for **13a**,**b**,**14a**,**b**,**15a**,**b**,**16**, C± 0.35, H±0.20, N±0.19.

13a

IR (KBr),: 3232, 3071, 2974, 2932, 1694, 1621,1558, 1524, 1455, 1364, 1306, 1169, 765, 699 cm^{-1}.

Table 6 ^{1}H and ^{13}C NMR Data of Compounds **13-16**

Product	^{1}H NMR ($CDCl_3$), δ *J* (Hz)	^{13}C NMR ($CDCl_3$), δ *J* (Hz)
13a	1.54 [s, 9 H, $C(CH_3)_3$], 2.27 (s, 3 H, CH_3), 2.51 (dd, 1 H, *J* = 4.4, 15.9 Hz, CHHC=O), 2.74 (dd, 1 H, *J* = 14.5, 15.9, Hz, CHHC=O), 4.71 (dd, 1 H, *J* = 4.4, 14.5 Hz, CH), 5.35 (br s, 1 H, NH), 7.34–7.40 (m, 5 H, C_6H_5)	21.3 (CH_3), 28.4 [$C(CH_3)_{,3}$], 43.6 (CH_2C=O), 57.2 (CH), 80.4 [$C(CH_3)_{,3}$], 106.5 (HN–C=C), 126.6 128.8 129.1 (CHAr), 139.1 (CAr), 163.7 (CO_2t-Bu), 165.9 (HN–C=C), 187.6 (C=O),
13b	1.26 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.53 [s, 9 H, $C(CH_3)_3$], 2.43 (dd, 1 H, *J* = 4.7, 15.9 Hz, CHHC=O), 2.59 (m, 2 H, CH_2CH_3), 2.63 (dd, 1 H, *J* = 14.3, 15.9 Hz, CHHC=O), 4.65 (dd, 1 H, *J* = 4.7, 14.3 Hz, CH), 5.68 (br s, 1 H, NH), 7.31–7.39 (m, 5 H, C_6H_5)	12.7 (CH_2CH_3), 27.3 (CH_2CH_3), 28.7 [$C(CH_3)_3$], 43.6 (CH_2C=O), 56.9 (CH), 80.4 [$C(CH_3)_3$], 105.9 (HN–C=C), 126.6 128.6, 129.1 (CHAr), 139.3 (CAr), 165.9 (CO_2t-Bu), 168.1 (HN–C=C), 187.9 (C=O)

Table 6 ^{1}H and ^{13}C NMR Data of Compounds **13-16** (continued)

Product	^{1}H NMR ($CDCl_3$), δ *J* (Hz)	^{13}C NMR ($CDCl_3$), δ *J* (Hz)
14a	1.52 [s, 9 H, $C(CH_3)_3$], 2.28 (s, 3 H, CH_3), 2.46 (dd, 1 H, *J* = 4.7, 15.9 Hz, C*H*HC=O), 2.62 (dd, 1 H, *J* = 13.9, 15.9 Hz, CH*H*C=O), 4.66 (dd, 1 H, *J* = 4.7, 13.9 Hz, CH), 5.72 (br s, 1 H, NH), 7.21–7.33 (m, 4 H, C_6H_4Cl)	21.2 (CH_3), 28.3 [$C(CH_3)_3$], 43.5 (CH_2C=O), 56.6 (CH), 80.5 [$C(CH_3)_3$], 106.7 (HN–C=*C*), 124.8, 126.8, 128.8, 130.4 (*C*HAr), 134.9, 141.3 (CAr), 163.7 (CO_2t-Bu), 165.7 (HN–*C*=C), 187.1 (C=O),
14b	1.23 (t, 3 H, *J* = 7.5 Hz, CH_2CH_3), 1.48 [s, 9 H, $C(CH_3)_3$], 2.31 (dd, 1 H, *J* = 5.2, 15.9 Hz, C*H*HC=O), 2.43 (dd, 1 H, *J* = 12.8, 15.9 Hz, CH*H*C=O), 2.58 (m, 2 H, CH_2CH_3), 4.56 dd, 1 H, *J* = 5.2, 12.8 Hz, CH), 6.55 (br s, 1 H, NH), 7.16–7.26 (m, 4 H, C_6H_4Cl)	12.9 (CH_2CH_3), 27.4 (CH_2CH_3), 28.2 [$C(CH_3)_3$], 43.2 (CH_2C=O), 55.9 (CH), 80.3 [$C(CH_3)_3$], 105.4 (HN–C=*C*), 124.8 126.7, 128.5, 130.2 (*C*HAr), 134.6, 141.5 (CAr), 165.7 (CO_2t-Bu), 169.1 (HN–*C*=C), 187.5 (C=O)
15a	1.50 [s, 9 H, $C(CH_3)_3$], 2.30 (s, 3 H, CH_3), 2.49 (dd, 1 H, *J* = 5.3, 15.9 Hz, C*H*HC=O), 2.61 (dd, 1 H, *J* = 12.5, 15.9 Hz, CH*H*C=O), 4.73 (dd, 1 H, *J* = 5.3, 12.5 Hz, CH), 6.79 (br s, 1 H, NH), 7.29 (dd, 1 H, *J* = 4.9, 7.8 Hz, ArH), 7.68 (d, 1 H, *J* = 7.8 Hz, ArH), 8.52 (m, 2 H, ArH)	21.3 (CH_3), 28.4 [$C(CH_3)_3$], 42.9 (CH_2C=O), 54.3 (*C*H), 80.5 [$C(CH_3)_3$], 106.2 (HN–C=*C*), 123.9, 134.4 (*C*HAr), 135.0 (CAr), 148.4, 149.8 (*C*HAr), 164.7 (CO_2t-Bu), 165.6 (HN–*C*=C), 187.0 (C=O)
15b	1.27 (t, 3 H, *J* = 7.5 Hz, CH_2CH_3), 1.53 [s, 9 H, $C(CH_3)_3$], 2.42 (dd, 1 H, *J* = 5.7, 15.9 Hz, C*H*HC=O), 2.51 (dd, 1 H, *J* = 11.7, 15.9 Hz, CH*H*C=O), 2.55 (m, 2 H, CH_2CH_3), 4.75 (dd, 1 H, *J* = 5.7, 11.7 Hz, CH), 5.81 (br s, 1 H, NH), 7.33 (dd, 1 H, *J* = 4.9, 7.8 Hz, ArH), 7.70 (d, 1 H, *J* = 7.8 Hz, ArH), 8.58 (m, 2 H, ArH)	13.0 (CH_2CH_3), 27.4 (CH_2CH_3), 28.2 [$C(CH_3)_3$], 42.8 (CH_2C=O), 54.0 (*C*H), 80.4 [$C(CH_3)_3$], 105.7 (HN–C=*C*), 123.8 134.3 (*C*HAr), 135.2 (CAr), 148.2, 149.6 (*C*HAr), 165.6 (CO_2t-Bu), 168.9 (HN–*C*=C), 187.2 (C=O)
16	1.51 [s, 9 H, $C(CH_3)_3$], 2.71 (s, 3 H, CH_3), 2.39 (dd, 1 H, *J* = 11.2, 15.8 Hz, C*H*HC=O), 2.52 (dd, 1 H, *J* = 5.1, 15.8 Hz, CH*H*C=O), 2.85 (dd, 1 H, *J* = 8.4, 13.4 Hz, C*H*HPh), 2.91 (dd, 1 H, *J* = 6.1, 13.4 Hz, CH*H*Ph), 3.84 (m, 1 H, CH), 5.43 (br s, 1 H, NH), 7.17–7.36 (m, 5 H, C_6H_5)	21.5 (CH_3), 28.3 [$C(CH_3)_3$], 39.4 (CH_2Ph), 40.5 (CH_2C=O), 52.8 (CH), 79.9 [$C(CH_3)_3$], 104.8 (HN–C=*C*), 126.9, 128.7, 129.1 (*C*HAr), 136.3 (CAr), 164.7 (CO_2t-Bu), 165.8 (HN–*C*=C), 188.3 (C=O)

2-Alkyl and 2-Aryl-6-alkyl-1,2-dihydro-1*H*-pyridin-4-one 17,18,19,20; General Procedure

To a stirred soln of tetrahydropyridinone **13**, **14**, **15** or **16** (5 mmol), in CH_2Cl_2 (10 mL), was added TFA (3.85 mL, 50 mmol), and the mixture was heated at 50 °C. After completion (4 h monitored by TLC analysis), the reaction mixture was neutralized with sat. aq K_2CO_3 and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried ($CaCl_2$) and concentrated in vacuo. The crude product was chromatographed on silica gel eluting with variable amounts of EtOAc–MeOH to give the pure compound. The ^{1}H and ^{13}C NMR data of **17,18,19,20** are recorded in Table 7. Satisfactory microanalyses were obtained for **17a**,**b,18a**,**b,19a**,**b**,**20** C ± 0.40, H ± 0.18, N ± 0.20.

17b

IR (KBr),: 3218, 3060, 2965, 2925, 2878, 1616, 1601, 1532, 1450, 1351, 1264, 1237, 1107, 769, 702 cm^{-1}.

Table 7 ^{1}H and ^{13}C NMR Data of Compounds **17**[a] **18**, **19**, **20**

Product	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ, *J* (Hz)
17b	1.19 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 2.28 (q, 2 H, *J* = 7.6 Hz, CH_2CH_3), 2.42 (dd, 1 H, *J* = 4.9, 16.2 Hz, C*H*HC=O), 2.62 (dd, 1 H, *J* = 14.5, 16.2 Hz, CH*H*C=O), 4.67 (dd, 1 H, *J* = 4.9, 14.5 Hz, CH), 5.04 (s, 1 H C=C*H*), 5.15 (br s, 1 H, NH), 7.31–7.40 (m, 5 H, C_6H_5)	11.7 (CH_2CH_3), 27.8 (CH_2CH_3), 43.4 (CH_2C=O), 57.9 (*C*H), 97.2 (C=*C*H), 126.5, 128.1, 128.7 (*C*HAr), 140.2 (CAr), 167.8 (*C*=CH), 191.9 (C=O)
18a	1.98 (s, 3 H, CH_3), 2.47 (dd, 1 H, *J* = 4.8, 16.0 Hz, C*H*HC=O), 2.60 (dd, 1 H, *J* = 14.2, 16.0 Hz, CH*H*C=O), 4.69 (dd, 1 H, *J* = 4.8, 14.2 Hz, CH), 4.98 (s, 1 H, C=CH), 5.34 (br s, 1 H, NH), 7.24–7.39 (m, 5 H, C_6H_5)	21.2 (CH_3), 43.2 (CH_2C=O), 57.9 (CH), 99.9 (C=*C*H), 124.6, 126.8, 128.6, 130.6 (*C*HAr), 134.8, 142.2 (CAr), 162.4 (*C*=CH), 191.5 (C=O)
18b	1.19 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 2.29 (q, 2 H, *J* = 7.6 Hz, CH_2CH_3), 2.37 (dd, 1 H, *J* = 5.0, 16.1 Hz, C*H*HC=O), 2.50 (dd, 1 H, *J* = 13.8, 16.1 Hz, CH*H*C=O), 4.62 (dd, 1 H *J* = 5.0, 13.8 Hz, CH), 4.98 (s, 1 H, C=CH), 5.63 (br s, 1 H, NH), 7.24–7.36 (m, 4 H, C_6H_4Cl)	11.7 (CH_2CH_3), 27.9 (CH_2CH_3), 43.4 (CH_2C=O), 57.6 (CH), 97.8 (C=*C*H), 124.8, 126.7, 128.4, 130.2 (*C*HAr), 134.6 142.4 (CAr), 167.7 (*C*=CH), 191.5 (C=O)

Table 7 ^{1}H and ^{13}C NMR Data of Compounds **17**[a] **18**, **19**, **20** (continued)

Product	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ, *J* (Hz)
19a	2.02 (s, 3 H, CH_3), 2.42 (dd, 1 H, *J* = 5.3, 16.2 Hz, C*H*HC=O), 2.55 (dd, 1 H, *J* = 13.3, 16.2 Hz, CH*H*C=O), 4.69 (dd, 1 H, *J* = 5.3, 13.3 Hz, CH), 4.98 (s, 1 H, Hz, C=CH), 6.07 (br s, 1 H, NH), 7.26 (dd, 1 H, *J* = 4.9, 7.8 Hz, ArH), 7.68 (d, 1 H, *J* = 7.8 Hz, ArH), 8.53 (d, 1 H, *J* = 4.9 Hz, ArH), 8.57 (s, 1 H, ArH)	21.0 (CH_3), 42.7 (CH_2C=O), 55.6 (CH), 99.6 (C=*C*H), 123.9, 134.6 (*C*HAr), 136.0 (CAr), 147.9, 149.2 (*C*HAr), 162.9 (*C*=CH), 190.9 (C=O)
19b	1.21 (t, 3 H, *J* = 7.5 Hz, CH_2CH_3), 2.31 (q, 2 H, *J* = 7.5 Hz, CH_2CH_3), 2.51 (dd, 1 H, *J* = 4.6, 16.1 Hz, C*H*HC=O), 2.65 (dd, 1 H, *J* = 13.4, 16.1 Hz, CH*H*C=O), 4.75 (dd, 1 H, *J* = 4.6, 13.4 Hz, CH), 5.09 (s, 1 H, Hz, C=C*H*), 5.20 (br s, 1 H, NH), 7.34 (dd, 1 H, *J* = 4.8, 7.8 Hz, ArH), 7.75 (d, 1 H, *J* = 7.8 Hz, ArH), 8.63 (m, 2 H, ArH)	11.6 (CH_2CH_3), 27.5 (CH_2CH_3), 42.3 (CH_2C=O), 54.7 (CH), 96.6 (C=*C*H), 123.3, 134.0 (*C*HAr), 135.7 (*C*Ar), 147.8 148.7 (*C*HAr), 168.6 (*C*=CH), 190.4 (*C*=O)
20	1.91 (s, 3 H, CH_3), 2.28 (dd, 1 H, *J* = 11.6, 16.1 Hz, C*H*HC=O), 2.39 (dd, 1 H, *J* = 5.1, 16.1 Hz, CH*H*C=O), 2.86 (dd, 1 H, *J* = 6.2, 13.5 Hz, C*H*HPh), 2.91 (dd, 1 H, *J* = 7.9, 13.5 Hz, CH*H*Ph), 3.81 (m, 1 H, CH), 4.92 (s, 1 H, C=CH), 5.54 (br s, 1 H, N*H*), 7.16–7.33 (m, 5 H, C_6H_5)	20.9 (CH_3), 39.9 (CH_2Ph), 40.6 (CH_2C=O), 54.1 (CH), 98.8 (C=*C*H), 126.8, 128.7, 129.0 (*C*HAr), 136.7 (CAr), 162.2 (*C*=CH), 191.9 (C=O)

[a] Description of **17a** was already published.[14]

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